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CERTIFICATE OF MAILING

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Date: November 27, 2001 Susan Dolci

Susan Dolci

RLL-178US

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

Applicant: Kumar *et al.*

Examiner: TBA

Application No.: 09/888,268

Group Art Unit: 1614

Filing Date: June 22, 2001

For: BIOAVAILABLE DOSAGE FORM OF LORATADINE

CLAIM OF PRIORITY UNDER 35 USC §119
AND SUBMISSION OF PRIORITY DOCUMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Applicants, by and through their attorney, hereby claim the priority of Indian Patent Application No. 651/Del/2000 filed July 17, 2000, a certified copy of which is submitted herewith.

Respectfully submitted,

KUMAR *et al.*

By: _____
Jayadeep R. Deshmukh, Reg. No. 34,507

Date: November 27, 2001

Ranbaxy Pharmaceuticals Inc.
600 College Road East, Suite 2100
Princeton, New Jersey 08540
Tel: (609) 720-5608
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GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY,
PATENT OFFICE, DELHI BRANCH
W-5, WEST PATEL NAGAR,
NEW DELHI-110 008.

I the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the Application and Complete Specification filed in connection with Application for Patent No. ***651/Del/2000*** *dated* ***17th July 2000.***

Witness my hand this 06th day of November 2001.

(H.C. BAKSHI)
Deputy Controller of Patents & Designs.

FORM 3 A

The Patents Act, 1970

COMPLETE SPECIFICATION
(See Section 10)

PROCESS FOR THE PREPARATION OF A BIOAVAILABLE DOSAGE FORM OF LORATADINE

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

6. Following declaration was given by the inventors in the convention country:

We, PANANCHUKUNATH MANOJ KUMAR, DINSHEET GUPTA, RAJIV MALIK of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention in the convention country declare that the applicants herein, **Ranbaxy Laboratories Limited**, 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representative.

a.

(PANANCHUKUNATH MANOJ KUMAR)

b. Dinsheet

(DINSHEET GUPTA)

c. Rajiv Malik

(RAJIV MALIK)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Followings are the attachment with the application:

a. Complete Specification (3 copies)

b. Drawings (3 copies)

c. Statement and Undertaking on FORM – 3

d. Fee Rs.5,000/- (Rupees Five Thousand only..) in cheque bearing No. 669828 dated 15.07.2000 on ANZ Grindlays Bank.

We request that a patent may be granted to us for the said invention.

Dated this 15th day of **July**, 2000.

For Ranbaxy Laboratories Limited

Sd/-

(S K PATAWARI)
Company Secretary

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 5 (2), 7, 54 and 135 and rule 33A)

17 JUL 2000

1 We, **RANBAXY LABORATORIES LIMITED,** a Company incorporated under the Companies Act, 1956 of 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"PROCESS FOR THE PREPARATION OF A BIOAVAILABLE DOSAGE FORM OF LORATADINE"**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. PANANCHUKUNATH MANOJ KUMAR
b. DINSHEET GUPTA
c. RAJIV MALIK

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. That we are the assignee or legal representative of the true and first inventors.

5. That our address for service in India is as follows:

DR. BRIJ KHERA
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18,
Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana).
INDIA.
Tel. No. (91-124) 6342001 – 10
Fax No. (91-124) 6342027

The present invention relates to a process for the preparation of a bioavailable oral dosage form of loratadine.

Loratadine or ethyl 4-(8-chloro-5,6-dihydro-11H-benzo[5,6] cyclohepta [1,2-b] pyridin -11-ylidene)-1-piperidine carboxylate is useful as an antihistamine. It is disclosed in US Pat. No. 4,282,233 assigned to Schering Corporation.

Loratadine is particularly advantageous for use of an antihistamine compared to other drugs of the same class as it is administered only once daily and has little or no sedative effects. It is therefore preferred for use by patients who have to perform mental or physical tasks requiring a high level of concentration. Loratadine however poses problems to the formulator as it has low solubility in water and therefore shows poor bioavailability characteristics.

It is an objective of the present invention to provide a process for the preparation of a bioavailable oral dosage form of loratadine, that is bioequivalent to commercially available formulation and falls within the prescribed limits set by various International Regulatory Agencies.

Accordingly, the present invention provides a process for the preparation of a bioavailable oral dosage form of loratadine, comprising the step of milling the drug to reduce its particle size, such that the average particle size ranges from about 0.1 microns to 15 microns and to increase its surface area to between 1-2 sq m/g.

It is observed that the particle size and the surface area of loratadine is critical in achieving bioequivalence against the commercially available formulation "Claritin", marketed by Schering Corporation. The particle size of the drug is reduced thereby increasing its surface area using any of the conventional milling techniques known in the art. These include the use of ball mill, cad mill, multi mill, air jet mill etc.

In preferred embodiments of the invention, the size of the drug is reduced such that the average particle size ranges between 1 microns to 10 microns. The surface area of the milled drug is maintained between 1 and 2 sq m / g.

The milled drug is then formulated into a suitable dosage form such as tablet, capsule, syrup, suspension etc. In preferred embodiments the pharmaceutical dosage form is a tablet. The milled drug is mixed with pharmaceutically acceptable excipients such as fillers, binders and lubricants and further processed using processes conventionally known in the art such as direct compression, compaction or wet granulation.

The fillers employed in the present invention preferably comprises a pharmaceutically acceptable saccharides, including monosaccharides, a disaccharides, and polysaccharides, polyhydric alcohols, or cellulose ethers and mixtures thereof. Examples of suitable pharmaceutical fillers include sucrose, dextrose, lactose, microcrystalline cellulose, fructose, xylitol, sorbitol, hydroxypropyl methylcellulose, mixtures thereof and the like. However, it is preferred that a soluble pharmaceutical filler such as lactose, dextrose, sucrose, or mixtures thereof be used.

The binders used in accordance with the present invention are those conventionally used in the art may be selected from the group consisting of gums such as karaya gum and locus bean gum, starch, polyvinylpyrrolidones etc. The lubricants are selected from amongst those conventionally used in the art such as magnesium stearate, zinc stearate, talc, tristearin, tripalmitin, polyethylene glycols, waxes, hydrogenated oils, aerosil and mixtures thereof.

Investigations were conducted in order to determine the effect of particle size and surface area on the bioavailability of loratadine. The blood levels of the drug were compared with that of the commercially available formulation of loratadine sold under the trade name of "Claritin". The area under the plasma concentration (loratadine) vs time curve (AUC) was determined between time "0" and time "t" to give the $AUC_{(0-t)}$ values and was then extrapolated to infinity (α) to calculate the value till there was no more drug in the plasma. This value is reported as $AUC_{(0-\alpha)}$. The maximum plasma concentration (Cmax) was also determined for each subject after each treatment.

The following examples further illustrates the invention but are not intended to limit the scope of the invention.

EXAMPLE 1

Tabl 1.1

Ingredients	Mg/Tab
Loratadine	10.0
Lactose	86.25
Starch	1.50
Pregelatinised starch	1.50
Magnesium stearate	0.75
Total	100.0mg

The particle size of loratadine was 90% below 47.2 microns and 50% below 10.7 microns. The surface area was 1.126 sq m/g. The active and the inactive excipients are mixed and compressed to tablets. The tablets released more than 90% of the content in 0.1N HCl in USP apparatus I at 50 rpm.

The formulation was subjected to a two way cross over bioequivalence study with "Claritin" (which was the reference product). Eighteen normal, male subjects were enrolled in each study. Whole blood samples were drawn at selected times following each treatment. Blood levels of the drug for both test and reference were determined and compared for the two critical parameters of AUC and Cmax (Table 1.1). Test is the formulation made according to present invention and reference is the formulation of loratadine sold under the trade name of "Claritin".

Table 1.2

	$AUC_{(0-t)}$	$AUC_{(0-\alpha)}$	C_{max} (μg/ml)
Test/ Reference (%)	81.5	85	87.7

As can be seen when the particle size of loratadine was 90% below 47 microns, the formulation was only around 80% bioavailable as compared to the commercially available formulation of loratadine sold under the trade name "Claritin".

EXAMPLE 2

Table 2.1

The process of granulation was changed from direct compression to wet granulation to study its effect, if any, on the bioavailability of the drug.

Ingredients	Mg/Tab
Loratadine	10.0
Lactose	86.50
Starch	1.50
Pregelatinised starch	1.50
Magnesium stearate	0.50
Total	100.0mg

The particle size of loratadine was 90% below 47.2 microns and 50% below 10.7 microns and the surface area was 1.126 sq m/gm. The drug was mixed with the inactive excipients, and granulated using water. The granules were dried and the tablets were compressed. The tablets released 90% of the drug in 0.1 NHCl in USP apparatus 2 within 30 minutes.

This formulation was subjected to a two way cross over bioequivalence study with "Claritin" on 18 normal male subjects as described in Example 1.

Table 2.2

	$AUC_{(0-t)}$	$AUC_{(0-\alpha)}$	C_{max} (µg/ml)
Test/ Reference (%)	74.8	85.1	67.5

Once again the bioavailability of the drug in our formulation was low compared to that of "Claritin", indicating that changing the processing conditions does not improve the bioavailability characteristics of the drug.

EXAMPLE 3

Tabl 3.1

As loratadine of the larger particle size showed lower bioavailability as compared to the commercially available product "Claritin", it was decided to investigate the effect of reduction of particle size of the loratadine on its bioavailability.

Ingredients	Mg/Tab
Loratadine	10.0
Lactose	79.75
Starch	7.5
Pregelatinised starch	2.0
Magnesium stearate	0.75
Total	100.0mg

The particle size of loratadine was 90% below 10 microns and 50% below 5 microns and the surface area was 1.54 sq m/g. The drug was mixed with the inactive excipients, granulated using water, the granules were dried, lubricated and then compressed to tablets.

The tablets released more than 90% of the drug in 0.1 NHCl in USP apparatus 2 within 30 minutes. The formulation was subjected to a two way crossover bioequivalence study on 20 healthy, male subjects as described in Example 1.

Table 3.2

	$AUC_{(0-t)}$	$AUC_{(0-\alpha)}$	C_{max} (µg/ml)
Test/ Reference (%)	100.7	91.7	95.5

As can be seen from the data, reduction in particle size of the drug led to a dramatic increase in the bioavailability of loratadine to equal that of the commercially available product "Claritin".

The next example further illustrates the importance of particle size and increased surface area on the bioavailability of loratadine.

EXAMPLE 4

Table 4.1

Ingredients	Mg/Tab
Loratadine	10.0
Lactose	80.60
Starch	7.5
Pregelatinised starch	2.0
Magnesium stearate	0.50
Total	100.0mg

The particle size of loratadine was almost similar to that used in example 3 i.e. 90% below 9 microns and 50% below 6 microns but the surface area at 2.042 sq mg/g was larger than that of loratadine used in Example 3. All the active and inactives were mixed and granulated using water. The granules were dried and compressed to tablets. The tablets released 90% of the drug in 0.1 NHCl in USP apparatus 2 within 45 minutes.

The formulation was subjected to a two way crossover study on 11 normal, healthy, male subjects as described in Example 1.

Table 4.2

	$AUC_{(0-t)}$	$AUC_{(0-\alpha)}$	C_{max} (µg/ml)
Test/ Reference (%)	134	124	130

Increase in the surface area together with the reduction of particle size caused a dramatic increase in the bioavailability of the drug to almost 30% greater than that of the commercially available reference product.

These result emphasize the criticality of particle size and surface area of loratadine on its bioavailability.

WE CLAIM :

1. A process for the preparation of a bioavailable oral dosage form of loratadine comprising the step of milling the drug to reduce the particle size such that the average particle size ranges from about 0.1 microns to about 15 microns and the surface area between 1 and 2.5sqm/g.
2. A process as described in claim 1 wherein loratadine is milled using a ball mill, cad mill, air jet mill or a multimill.
3. A process as described in claim 1, wherein the particle size of loratadine is more preferably between about 1 micron to about 10 microns.
4. A process as described in claim 1, wherein the surface area of loratadine between 1.25 and 2.0 sqm/g.
5. A process as described in claim 1, wherein the milled drug is mixed with other pharmaceutically acceptable excipients belonging to the categories of fillers, binders and lubricants.
6. A process as described in claim 5, wherein the fillers used are selected from the group consisting of saccharides, polyhydric alcohols, celluloses and cellulose ethers.
7. A process as described in claim 5 wherein the fillers are preferably selected from lactose, dextrose, sucrose, microcrystalline celluloses, hydroxypropyl methyl cellulose and mixtures thereof.
8. A process as described in claim 5, wherein the binders are selected from the group consisting of starch, polyvinylpyrrolidone and gums.
9. A process as described in claim 5, wherein the lubricants are selected from the group consisting of talc, magnesium strearate, zinc stearate, tristearin, tripalmitin, polyethylene glycol, waxes, aerosil and mixtures thereof.
10. A process as described in claim 1, wherein the dosage form is formulated as a tablet, capsule or suspension.
11. The process for the preparation of a bioavailable oral dosage form of loratadine substantially as herein described and exemplified by the examples.

Dated this 17th day of **July, 2000**.

For Ranbaxy Laboratories Limited

(S K Patawari)
Company Secretary